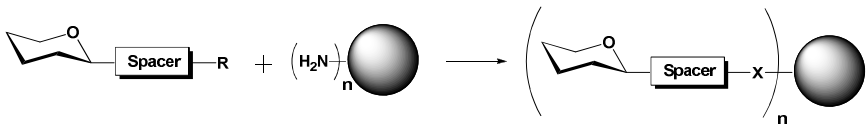
Abstract

From a historical perspective, no single class of organic compounds as sugar molecules has shared the same impact on the evolution of stereochemistry. As biological activity began to be associated with more complex natural products in the middle of the twentieth century, interest in sugars as small molecule polyols shifted to the study of polysaccharides and their degradation products.

A renaissance period for sugars is in full swing with the creation of new subdisciplines that bridge chemistry and biology. Sugar chemistry has emerged as a pivotal link between molecular recognition and biological events in conjunction with vital life processes.

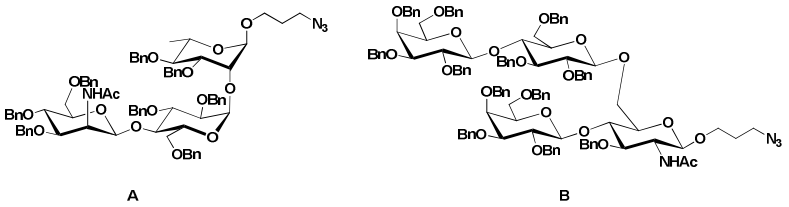
The preceding preamble to a sugar chemistry panorama was necessary to introduce this PhD work, based on glycochemistry, that has been planned, developed and realized paying attention to the biological impact of each synthesized compound. A common aspect, as indicates in the title "synthesis of immunologically relevant PAMAM-based glycodendrimers", is the preparation of oligosaccharide and their mimic structures which have been loaded on multibranched molecules (PAMAM dendrons) tested or to be tested towards immune system (Figure 1).

Figure 1



In Part 1 (Section 1 & 2) is described the preparation of PAMAM based glyconjugates that might be used as vaccines against pneumococcal diseases, a worldwide pathogenic problem. Starting from commercial available products as lactose and glucosamine, multistep sequences, characterized by higly regio- and stereoselective reactions, have permitted to obtain oligosaccharides **A** and **B** (Figure 2).

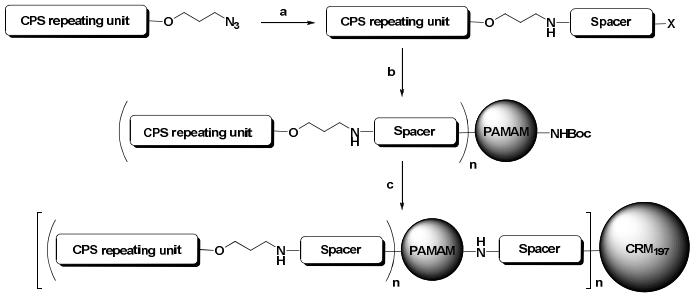
Figure 2



Trisaccharide **A** represents the repeating unit of capsular polisaccharide (CPS) of the *Streptococcus Pneumoniae 19F*. Tetrasaccharide **B** is the repeating unit of the *Streptococcus Pneumoniae 14* CPS. As represented in Figure 2, both oligosaccharide have an azidopropyl spacer on anomeric position that permits its elaboration and conjugation with dendritic matrices or directly with immunogenic proteins, as CRM_{197}. As a first attempt to *SP* glycoconjugate preparation, trisaccharide **A** has been

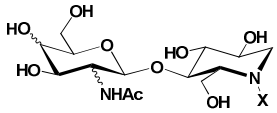
elaborated on the spacer (a, Scheme 1) and loaded an a PAMAM matrix (b, Scheme 1). Finally conjugation with immunogenic CRM_{197} has been directly made on **A** and also on *SP19F* glycodendrimers (c, Scheme 1). Biological tests on a possible activity towards immune system are now running.

Scheme 1



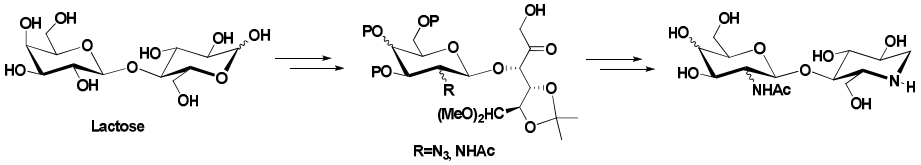
In Part 2 is presented the synthesis of various 1-deoxynojirimycin (DNJ) based iminosugars as activators of Natural Killer cells, lymphoid cells that represent an important protection against pathogenic agents (Figure 3). A common structural aspect is the presence of an *N*-acetylhexosaminyl unit linked with the most studied iminosugar, the DNJ.

Figure 3



As shown in Scheme 2, all DNJ containing disaccharide mimics have been prepared starting from cheap commercial lactose through a first elaboration of non-reducing portion, followed by a standardized manipulation of *gluco* part. The aminocyclization step represents the key reaction that transforms the protected glucose portion into DNJ one.

Scheme 2



Two representatives of this compound family have been tested towards NKR-P1 and CD69 receptors and the most relevant result has been the NK stimulation action of DNJ itself. This study on NK carbohydrate ligands has been completed by the preparation of various PAMAM glycodendrimers loaded with NK cell activators to be tested in a multivalence effect study.